## REMARKS

Claims 6-22 and 24-29 are pending.

**INVENTION IS ENABLED**

Claims 6-22 and 24-29 have been rejected under 35 USC 112, first paragraph, as allegedly not being enabled by the specification. The rejection is respectfully traversed.

In the instant case applicant has disclosed a genus of compounds, has described how to make such compounds, has stated what diseases they are useful for treating, has taught how to formulate and administer such compounds, as well as their dosages. And yet the Office asserts its "position that one skilled in the art could not practice the invention without undue experimentation." (Office Action, page 3). In view of the extensive disclosure in this application, the rejection's assertion of undue experimentation presumably means that the Office does not believe that the compounds of claims 19-22 and 24-29 have any activity and does not believe that the compounds recited in claims 6-22 are useful in treating the recited diseases when administered as described in the specification.

The Office bears the burden of establishing that an invention does not satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. As stated by the CCPA in In re Marzocchi:

> "As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

(In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, ___) (underlining added). It is not sufficient for the Office to simply assert that it doubts the correctness of the statements in the disclosure. The Office must back up its doubts with evidence or reasoning. Again from In re Marzocchi:

> "In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement."

(In re Marzocchi, 439 F.2d at 224, 169 USPQ at ___) (internal citations omitted) (underlining added). The only reasoning presented by the rejection is the alleged unpredictability of the pharmaceutical art in general. The rejection stated:

> "It is generally recognized in the art that biological compounds often react unpredictably under different circumstances. The relative skill of the artisan or [sic] the unpredictability of the pharmaceutical art is very high."

(Office Action, page 3) (internal citations omitted). But that does not constitute adequate reasoning to support an enablement rejection. If the mere assertion that the pharmaceutical art is unpredictable would be accepted as sufficient reasoning, it would mean that in the case of all biological and pharmaceutical inventions applicants would have the burden of demonstrating enablement rather than the Office having the burden of demonstrating that an invention is not enabled. And that would be contrary to the law as articulated in Marzocchi above.

With regard to the scope of the compounds, the rejection has taken the position that only 4-(3-(2,6-Dimethylbenzyloxy)-phenyl)-4(R)-hydroxybutanoic acid is enabled. WO 02/100341 (of record) discloses a genus of compounds that is the same as those claimed in the subject application except that they are oxo-substituted instead of hydroxy-

substituted. WO 02/100341 tested and demonstrated the activity of a representative number of compounds having different values for the variables recited in the genus. It would not have been possible to predict that the hydroxy analogs of the oxo-substituted compounds disclosed in WO 02/100341 would have the same activities, as explained below in response to the obviousness rejection. But once applicants tested the hydroxy analog of one of the compounds disclosed in WO 02/100341 and demonstrated that it has similar activity as its oxo-substituted counterpart, the person of ordinary skill in the art would accept that other hydroxy-substituted analogs would also possess activity similar to the corresponding oxo-substituted compounds taught in WO 02/100341.

Applicants have asserted (US 2006/0014784, paragraph [0019]) that both the (R) enantiomer and the (S) enantiomer are active. The rejection has not provided any specific reason for doubting that assertion, only a general assertion of unpredictability in the pharmaceutical art. It is true that sometimes only one enantiomer of a given compound possesses the desired activity, but in other cases both enantiomers are active. For example, Child, et al. reported that in the case of the 4-hydroxybutanoic acid analog of fenbufen both the *d* enantiomer and the *l* enantiomer appeared to have comparable activity with the racemate. (Child, et al., Fenbufen, a New Anti-Inflammatory Analgesic: Synthesis and Structure-Activity Relationships of Analogs" J. Pharm. Sci. (1977) 66(4): 466-476 at 470, right column, sixth full paragraph. Structures of compounds LV, LVI and LVII are shown in Table III on page 471.) (enclosed with the Form PTO/SB/08a submitted concurrently herewith). Applicants submit that the skilled artisan would accept applicants' assertion that both the (R) and (S) enantiomers of the claimed compounds possess the desired activities.

The examples show the results of testing a compound of this invention in mouse experiments that are models for disorders that are insulin resistance syndromes and consequences of chronic hyperglycemia. (See US 2006/0014784, paragraphs [0203] and [0204] and Examples). Thus, persons of skill in the art would accept that the compounds of this invention are useful in treating the claimed disorders.

The rejection singled out cachexia as a disorder whose treatment is allegedly not enabled by the specification. Compounds of the invention reverse insulin resistance associated with diabetes and metabolic disease. While insulin resistance is often associated with obesity (especially in the setting of concurrent hyperinsulinemia), insulin resistance is also a component of disease states involving weight loss (abstract of Wedick NM, et al. (2001) Insulin resistance precedes weight loss in adults without diabetes. American Journal of Epidemiology 153:1199-1205; abstract of Rofe et al., (1994) Altered insulin response to glucose in weight-losing cancer patients. Anticancer Research 14:647-650.) (enclosed with the Form PTO/SB/08a submitted concurrently herewith).

Cachexia involves muscle wasting associated with disease states including cancer, systemic inflammation, infection and aging. A key element in cachexia is impaired insulin sensitivity, especially in muscle. Cancer patients with weight loss often have impaired glucose tolerance, a sign of insulin resistance (Rofe et al., 1994 (abstract); abstract of Tayek, (1992) A review of cancer cachexia and abnormal glucose metabolism in humans with cancer. Journal of the American College of Nutrition 11:445-456) (enclosed with the Form PTO/SB/08a submitted concurrently herewith). Insulin signaling in muscle inhibits proteolysis; either insulin deficiency or insulin resistance disinhibits proteolysis, leading to loss of muscle mass. Combined insulin deficiency and resistance occurs in uncontrolled Type 1 diabetes and in cancer cachexia.

An additional link between insulin and body weight dysregulation in both obesity and cachexia is tumor necrosis factor alpha (TNFα). TNFα was originally known as "cachectin" due to its role in cachexia or muscle wasting and weight loss induced by infection and cancer. However, TNFα expressed in adipose tissue induces insulin resistance and obesity (abstract of Argiles et al., (1997) Journey from cachexia to obesity by TNF. The FASEB Journal 11:743-751) (enclosed with the Form PTO/SB/08a submitted concurrently herewith). TNFα is one of the causes of insulin resistance in both diabetes and cachexia (abstract of de Alvaro et al., (2004) Tumor Necrosis Factor α

produces insulin resistance in skeletal muscle by activation of Inhibitor κB Kinase in a p38 MAPK-dependent manner (2004) Tumor Necrosis Factor α produces insulin resistance in skeletal muscle by activation of Inhibitor κB Kinase in a p38 MAPK-dependent manner) (enclosed with the Form PTO/SB/08a submitted concurrently herewith).

Compounds of the invention reverse insulin resistance associated with diabetes and obesity, and can attenuate weight gain in that situation. However, by addressing insulin resistance in situations where muscle wasting is occurring, including insulin deficiency states, compounds of the invention attenuate the severity of cachexia, both prophylactically and therapeutically.

In view of the foregoing, applicants respectfully submit that the enablement rejection has been overcome.

**INVENTION IS NONOBVIOUS**

Claims 6-22 and 24-29 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over WO 02/100341 (Sharma) in view of U.S. Patent No. 6,307,080 (Pischel) and U.S. Patent No. 5,665,387 (Mathieu). The rejection is respectfully traversed.

WO 02/100341 discloses certain compounds substituted by an oxo group at the final position of the acid, for example 4-(3-(2,6-Dimethylbenzyloxy)phenyl)-4-oxobutyric acid. The rejection acknowledges that WO 02/100341 does not disclose any compounds in which the final position of the acid is hydroxy-substituted. The rejection relies on the secondary references, Pischel et al. and Mathieu, et al., as allegedly showing that hydroxyl and keto are obvious variants.

Pischel discloses certain zinc pyruvate compounds. These compounds are said to be useful in treating diabetes, cold prophylaxis, virus inhibition, cytoprotection, as a microbicide, as a radical absorber, as a food supplement or supplement for the propylaxis and prevention of zinc deficiency syndromes. (Abstract). Pischel states, "The organic acid used can in principle be any physiologically safe carboxylic acid which may optionally be substituted with . . . keto or hydroxyl groups." (column 5, lines 7-10). Pischel tested for macrophage activation, for cytokines, for inhibition of NO secretion, and for antiviral activity. But Pischel did not test any compound for its usefulness in treating diabetes. Moreover Pischel did not test any hydroxy-substituted compounds for any activity. Accordingly, the disclosures of Pischel on which the rejection relies are purely hypothetical.

Mathieu discloses the use of certain vitamin D analogues for treating autoimmune diseases such as Type 1 diabetes. Mathieu discloses a general formula with many variables and values for such variables. Mathieu actually tested two compounds: 1,25 Dihydroxy-Vitamin D3 ($1,25(OH)_2D_3$) and KH1060 ($1\alpha,25(OH)_2$-20-epi-22-oxa-24,26,27-trishomo vitamin D). But Mathieu did not test analogous compounds in which the only difference is that one is substituted by hydroxyl and the other is substituted by oxo at the same position.

In contrast, compounds in which the hydroxy analog of an oxo compound was actually demonstrated to lack the activity of the oxo compound were well known. To illustrate, copies of the following journal articles are enclosed with the Form PTO/SB/08a submitted concurrently herewith:

- Connolly, et al., J. Med. Chem. (2002) 45: 1348-1362.
- Flynn, et al., J. Med. Chem. (2002) 45: 2670-2673.

Compounds **22** and **41** of Connolly (Table 6 on page 1355) are analogous compounds. In compound **22**, X and Y together are =O. In compound **41** X is H and Y is OH. Connolly tested the ability of various compounds to inhibit Cytosolic Phospholipase $A_2$. Connolly found that "Simple changes to the highly potent keto-acid **22**, such as . . . reduction (**41** and **42**) . . . largely destroy activity (see Table 6)." (Connolly, page 1355, left column, last paragraph) (bolding in original).

Compounds **9** and **20** of Flynn (Table 1 on page 2671) are analogous compounds. In compound **9** Y is C=O. In compound **20** Y is CH(OH). The compounds shown in Table 1 "were evaluated for inhibition of tubulin assembly (Table 1). Those that displayed a significant inhibitory effect (defined as $IC_{50} < 5.0$ μM) were also examined for an inhibitory effect on the binding of [$^3$H]colchicine to tubulin. . . . These compounds were also evaluated for cytotoxicity against MCF-7 human breast carcinoma cells (Table 1)." (Flynn, page 2672, left column, first full paragraph). "Compound **9** was the most active" of all compounds tested in the inhibition of tubulin polymerization test. (Flynn, page 2672, second full paragraph. See also Table 1) (bolding in original). In contrast compound **20** had an $IC_{50} > 40$ μM, which did not meet the criteria for significant inhibitory effect in the inhibition of tubulin polymerization test. Similarly in the inhibition of MCF-7 cell growth test compound 9 had an $IC_{50}$ of 34 ± 10 nM, whereas compound **20** had an $IC_{50} > 1000$ nM.

The person of ordinary skill in the art would have given greater credence to the actual experimental evidence of nonequivalence in compounds differing only in having hydroxy or oxo at the same position as shown in Connolly et al. and Flynn et al. than to the hypothetical teachings of equivalence in Pischel et al. or to the less probative examples of Mathieu et al. Accordingly, the person of ordinary skill would not have predicted that the hydroxy-substituted compounds of the present invention would possess the same activity as their oxo-substituted analogs disclosed in WO 02/100341 with a reasonable expectation of success.

Moreover there are good theoretical reasons for not necessarily expecting oxo and hydroxy to be interchangeable. The substitution of the tetrahedral alcohol (i.e. hydroxy) for the planar carbonyl (i.e. oxo or keto) group alters the geometry, the H-bonding properties and the charge distribution of the molecule. Alcohols have both H-bond donor and acceptor properties, while an oxygen functionality at the final position of the acid acts as an H-bond acceptor but not as an H-bond donor. Therefore it could not have been reasonably predicted that the hydroxy-substituted compounds of the present invention would possess the same activity as their oxo-substituted analogs disclosed in WO 02/100341.

In view of the foregoing, applicants respectfully submit that the Section 103 rejection has been overcome.

**NO DOUBLE PATENTING**

Claims 6-22 and 24-29 have been provisionally rejected for alleged obviousness-type double patenting over claims 6-22 of copending Application No. 10/553,936 (the '936 application), claims 6-22 of copending Application No. 10/554,586 (the '586 application) and claims 1-66 of copending Application No. 11/535,779 (the '779 application) in view of U.S. Patent No. 5,604,225 (Reiffen), U.S. Patent No. 6,156,781 (Talley), U.S. Patent No. 5,665,387 (Mathieu), and Patent Publication No. US 2002/0028943. The double patenting rejections are respectfully traversed.

**Patentably Distinct from Application No. 10/553,936**

The claims in the '936 application recite compounds having an alkenyl double bond in the backbone of the molecule instead of a hydroxy substituent. The rejection relies on U.S. Patent No. 5,604,225 (Reiffen, et al.) and U.S. Patent No. 6,156,781 (Talley, et al.) for the proposition that hydroxy-substitution and an alkenyl double bond are obvious variants.

The substitution of the tetrahedral alcohol (i.e. hydroxy) for the planar alkenyl alters the geometry, the H-bonding properties and the charge distribution of the molecule. Alcohols have both H-bond donor and acceptor properties, while an alkenyl double bond has neither. Therefore it could not have been reasonably predicted that the hydroxy-substituted compounds of the present invention would possess the same activity as the reference compounds.

The rejection relies on the teaching of Reiffen that substituent $R_4$ can be, among other things, hydroxyl or alkenyl. But this teaching of Reiffen is not analogous to the difference between the compounds of the present invention and those of Reiffen. $R_4$ of Reiffen is a substituent. In the case where $R_4$ is alkenyl it is an alkenyl substituent. But in the '936 application the alkenyl is not a substituent. Rather it is a double bond in the backbone of the molecule, turning what would otherwise be an alkanoic acid moiety into an alkenyl acid moiety. Thus the alkenyl of Reiffen relied upon by the rejection is not analogous to or probative of the instant rejection. Moreover, Reiffen discloses a genus of compounds with a large number of variables. Reiffen did not test even a single compound for any activity.

The reliance of the rejection on Talley is similarly misplaced. Talley teaches that $R^4$ can be substituted by, among other things, hydroxyl or alkenyl. But this teaching of Talley is not analogous to the difference between the compounds of the instant invention and those of Talley. The alkenyl mentioned in the passage of Talley cited in the rejection is an alkenyl substituent. In conrast, in the '936 application the alkenyl is not a substituent. Rather it is a double bond in the backbone of the molecule, turning what would otherwise be an alkanoic acid moiety into an alkenyl acid moiety. Thus the alkenyl of Talley relied upon by the rejection is not analogous to or probative of the instant rejection.

Based on the nonanalogous teachings of Reiffen and Talley, applicants submit that the person of ordinary skill in the art would not have had a reasonable expectation of success from changing an alkenyl double bond in the backbone of the molecule as in the '936 application to a single bond in the backbone of the molecule and adding a hydroxy substituent.

**Patentably Distinct from Application No. 10/554,586 and No. 11/535,779**

The claims in the '586 application differ from the claims of the instant application in two ways. First, they are not hydroxy-substituted at the position adjacent to the central phenyl ring. Second, they are keto-substituted at the alpha position of the alkanoic acid. The claims in the '586 application recite compounds that are not hydroxy-substituted at the position adjacent to the central ring, but are keto-substituted at various positions.

The rejection relies on Patent Publication No. US 2002/0028943 (Griffin) and U.S. Patent No. 5,665,387 (Mathieu, et al.) for the proposition that alkyl, hydroxyl and keto are obvious equivalents.

Griffin discloses an enormously large genus of compounds with many variables. The passage cited by the rejection is nothing more than Griffin's definition of "substituted alkyl". Griffin did not test even a single compound for any activity. Accordingly, the disclosures of Griffin on which the rejection relies are purely hypothetical.

Mathieu discloses the use of certain vitamin D analogues for treating autoimmune diseases such as Type 1 diabetes. Mathieu discloses a general formula with many variables and values for such variables. Mathieu actually tested two compounds: 1,25 Dihydroxy-Vitamin D3 ($1,25(OH)_2D_3$) and KH1060 ($1\alpha,25(OH)_2$-20-epi-22-oxa-24,26,27-trishomo vitamin D). But Mathieu did not test analogous compounds in which the only difference is that one is substituted by hydroxyl and the other is substituted by oxo at the same position.

In contrast, compounds in which the hydroxy analog of an oxo compound was actually demonstrated to lack the activity of the oxo compound were well known. To illustrate, copies of the following journal articles are enclosed with the Form PTO/SB/08a submitted concurrently herewith:

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The person of ordinary skill in the art would have given greater credence to the actual experimental evidence of nonequivalence in compounds differing only in having hydroxy or oxo at the same position as shown in Connolly et al. and Flynn et al. than to the hypothetical teachings of equivalence in Griffin et al. or to the less probative examples of Mathieu et al. Accordingly, the person of ordinary skill would not have predicted that the hydroxy-substituted compounds of the present invention would possess the same activity as their oxo-substituted analogs claimed in the '586 application and the '779 application with a reasonable expectation of success.

Moreover there are good theoretical reasons for not necessarily expecting oxo and hydroxy to be interchangeable. The substitution of the tetrahedral alcohol (i.e. hydroxy) for the planar carbonyl (i.e. oxo or keto) group alters the geometry, the H-bonding properties and the charge distribution of the molecule. Alcohols have both H-bond donor and acceptor properties, while an oxygen functionality at the final position of the acid acts as an H-bond acceptor but not as an H-bond donor. Therefore it could not have been reasonably predicted that the hydroxy-substituted compounds of the present invention would possess the same activity as their oxo-substituted analogs claimed in the '586 application and the '779 application.

In view of the foregoing, applicants respectfully submit that the obviousness-type double patenting rejections have been overcome.

**CONCLUSION**

Reconsideration and withdrawal of all rejections and objections is respectfully requested.

No fee, other than the extension of time fee, is believed necessary in connection with the filing of this Amendment. If any additional fee is required, the Commissioner is hereby

authorized to charge the amount of such fee, or to refund any overpayment, to Deposit Account No. 50-1677.

Respectfully submitted,

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